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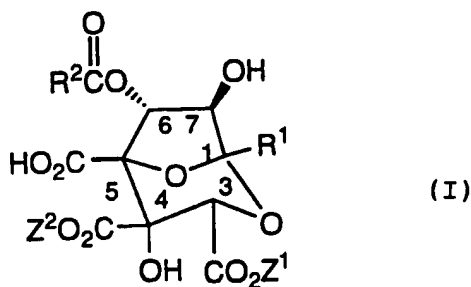
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/335, C07D 319/04		A1	(11) International Publication Number: WO 94/09774
			(43) International Publication Date: 11 May 1994 (11.05.94)
(21) International Application Number: PCT/US93/10164 (22) International Filing Date: 22 October 1993 (22.10.93) (30) Priority data: 966,764 26 October 1992 (26.10.92) US 966,971 26 October 1992 (26.10.92) US (60) Parent Applications or Grants (63) Related by Continuation US 966,764 (CIP) Filed on 26 October 1992 (26.10.92) US 966,971 (CIP) Filed on 26 October 1992 (26.10.92) (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only) : CHIANG, Yuan-Ching, P. [CN/US]; 17 Burnham Court, Scotch Plains, NJ 07076 (US). BIFTU, Tesfaye [US/US]; 108 Hyslip Avenue, Westfield, NJ 07090 (US). (74) Agent: DOLAN, Catherine, A.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: **BIOLOGICALLY ACTIVE COMPOUNDS AND PROCESS THEREFOR**



(57) Abstract

Disclosed herein are compounds of structural formula (I), and a process for making compounds of formula (I) involving selective saponification of the C-4 ester using Lewis acids such as thionyl chloride, tin (IV) chloride or hydrogen fluoride. The compounds of formula (I) are useful as cholesterol lowering agents.

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TITLE OF THE INVENTIONBIOLOGICALLY ACTIVE COMPOUNDS AND PROCESS
THEREFORBACKGROUND OF THE INVENTION

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Hypercholesterolemia is known to be one of the prime risk factors for ischemic cardiovascular disease, such as arteriosclerosis. Bile acid sequestrants have been used to treat this condition; they seem to be moderately effective but they must be consumed in large quantities, i.e. several grams at a time, and they are not very palatable.

10

MEVACOR® (lovastatin) and ZOCOR® (simvastatin), now commercially available, are members of a group of very active antihypercholesterolemic agents that function by limiting cholesterol biosynthesis by inhibiting the enzyme, HMG-CoA reductase.

15

Squalene synthase is the enzyme involved in the first committed step of the de novo cholesterol biosynthetic pathway. This enzyme catalyzes the reductive dimerization of two molecules of farnesyl pyrophosphate to form squalene. The inhibition of this committed step to cholesterol should leave unhindered biosynthetic pathways to ubiquinone, dolichol and isopentenyl t-RNA.

20

Previous efforts at inhibiting squalene synthase have employed pyrophosphate or pyrophosphate analogs containing compounds such as those described in P. Ortiz de Montellano, et al., J. Med Chem., 20, 243 (1977) and E.J. Corey and R. Volante, J. Am. Chem. Soc., 98, 1291 (1976). S. Biller (U.S. Patent 4,871,721) describes isoprenoid (phosphinylmethyl)phosphonates as inhibitors of squalene synthase.

25

Recently certain nonphosphorous containing inhibitors of squalene synthase have been isolated as natural products. These natural product inhibitors are described in US Patents 5,102,907; 5,132,320; 5,096,923; 5,026,554; 5,055,487; and 5,053,425. A need still remains for a more effective squalene synthase inhibitor, i.e. one that provides a greater antihypercholesterolemic effect and exhibits a good safety profile.

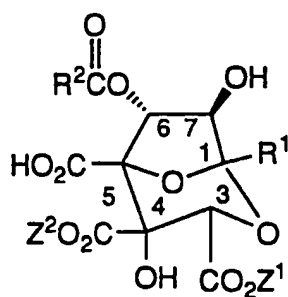
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The present invention is directed to semi-synthetic analogs of the above-noted natural products, and a novel process for making them.

DETAILED DESCRIPTION OF THE INVENTION

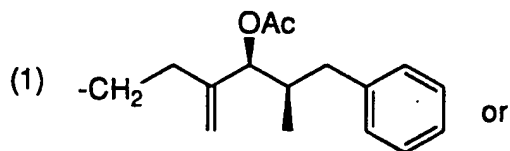
This invention relates to compounds of structural formula (I) which are useful as cholesterol lowering agents:



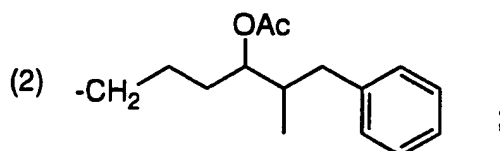
(I)

wherein:

R¹ is

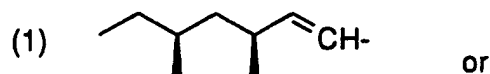


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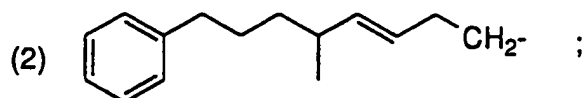


;

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R² is

5

Z¹ is C₁-3alkyl or -CH₂-CH=CH₂;

10

Z² is (1)  ;

wherein:

R³ is -H or C₁-4alkyl,

n is zero or 1, and

15

R⁴ is(a) C₁-5 alkyl,

(b) phenyl, or

(c) phenyl substituted with X and Y, defined below,

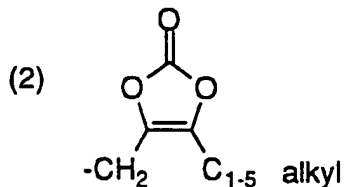
or, when R³ is C₁-4 alkyl, R³ and R⁴ are joined together to form

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a monocyclic or bicyclic ring system,

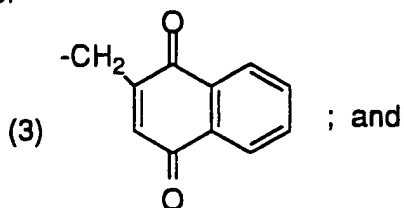
or, R⁴ is joined together with the carbon to which R³ is attached to form a monocyclic or bicyclic ring system, and R³ represents the bond between R⁴ and the carbon to which R³ is attached,

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or

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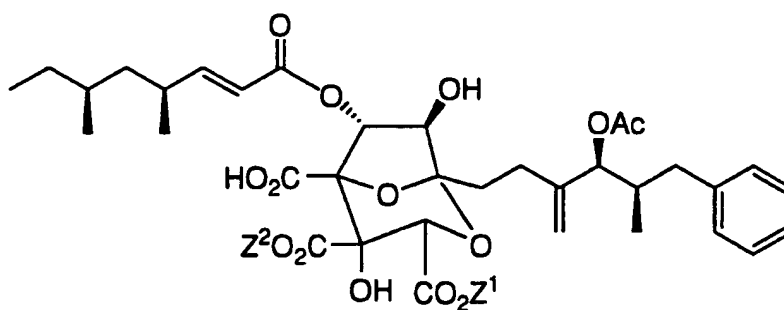
X and Y are each independently:

- (1) hydrogen,
- (2) hydroxy,
- (3) halogen,
- (4) trifluoromethyl,
- (5) C₁-4alkyl,
- (6) C₁-4alkyl-O-,
- (7) C₁-4alkyl-C(O)-O-,
- (8) -CO₂C₁-4alkyl,
- (10) -CO₂H, or
- (11) nitro;

or a pharmaceutically acceptable salt thereof.

Preferred compounds of this invention are depicted in
Tables 1 and 2, below.

TABLE 1

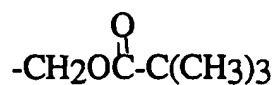


(II)

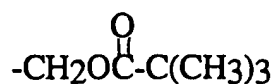
Z¹

Z²

1a) CH₃

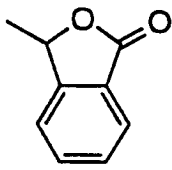
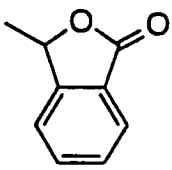
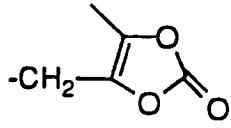


1b) -CH₂CH₃



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TABLE 1 Cont'd

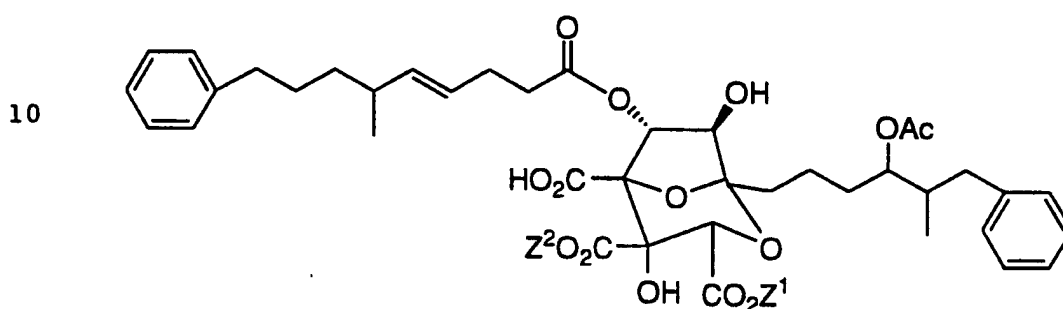
	<u>Z</u> ¹	<u>Z</u> ²
5	1c) -CH ₂ CH ₂ CH ₃	$\text{-CH}_2\text{OC(=O)C(CH}_3)_3$
	1d) -CH ₂ -CH=CH ₂	$\text{-CH}_2\text{OC(=O)C(CH}_3)_3$
	1e) -CH(CH ₃) ₂	$\text{-CH}_2\text{OC(=O)C(CH}_3)_3$
10	1f) -CH ₂ CH ₃	$\text{-CH(CH}_3\text{)OC(=O)OCH}_2\text{CH}_3$
	1g) -CH ₂ CH ₂ CH ₃	$\text{-CH(CH}_3\text{)OC(=O)OCH}_2\text{CH}_3$
15	1h) -CH ₂ CH ₃	$\text{-CH(CH}_3\text{)OC(=O)C(CH}_3)_3$
	1i) -CH ₂ CH ₂ CH ₃	$\text{-CH(CH}_3\text{)OC(=O)C(CH}_3)_3$
20	1j) -CH ₂ CH ₃	
25	1k) -CH ₂ CH ₂ CH ₃	
30	1l') -CH ₂ CH ₃	

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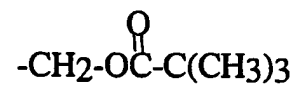

TABLE 1 Cont'd

\underline{Z}^1	\underline{Z}^2
1m) -CH ₂ CH ₂ CH ₃	

TABLE 2



(III)

\underline{Z}^1	\underline{Z}^2
2a) -CH ₂ CH ₃	
2b) -CH ₂ CH ₂ CH ₃	

Except where specifically defined to the contrary, the word "alkyl" includes both branched and straight chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, such as, e.g., methyl (Me), ethyl (Et), iso-propyl (i-Pr), and tert-butyl (t-Bu). Acyl, i.e. -COCH₃, is abbreviated herein as "Ac", phenyl is "Ph", and ethyl acetate is "EtOAc."

The compounds of formula I can be prepared from (1S, 3S, 4S, 5R, 6R, 7R)-1-[(4S)-acetoxy-3-methyl-ene-5-methyl-6-phenyl]-hexyl-4,6,7-trihydroxy-6-O-(4,6-dimethyl-2-octenoyl)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid (referred to herein as Compound IA), or (1S, 3S, 4S, 5R, 6R, 7R)-1-[(4)-acetoxy-5-methyl-6-phenyl]hexyl-4,6,7-tri-hydroxy-6-O-(6-methyl-9-phenyl-4-nonenoyl)-

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2,8-dioxabicyclo[3.2.1]-octane-3,4,5-tricarboxylic acid (referred to herein as Compound IC) according to the sequences described in Schemes A, B and C. The preparation of the starting materials, IA and IC, are described in U.S. Patents 5,096,923 and 5,102,907, respectively. Although Schemes A-C depict the use of Compound IA and derivatives thereof, the same methods can be used employing Compound IC and its derivatives. Furthermore, Scheme C, as well as Schemes A and B, can be used to make the compounds of the invention, but can also be used by one skilled in the art to synthesize a broader range of C-3, C-4 diester products. For example, one could use starting materials with a broader range of R¹ and R² groups and/or having an ether at the 7-position, or one could use other appropriate alcohols, alkyl halides, etc., to form a variety of esters at the C-3, C-4 and C-5 positions using the described methods.

Compounds are named in the examples and in some places throughout the description as ester derivatives at the C3, C4 and/or C5 carboxylic acid positions of compounds IA and IC as, e.g., IA-3-ethyl-4-pivaloyloxymethyl diester (Compound II in Table 1 wherein Z¹ is ethyl and Z² is pivaloyloxymethyl), and IC-3-n-propyl ester (Compound III in Table 2 wherein Z¹ is n-propyl and Z² is -H).

SCHEME A:

C-3 monoesters (1) may be prepared by several procedures. Stirring IA in an alcohol of formula Z¹-OH, wherein Z¹ is defined above, in the presence of an acid such as sulfuric acid or hydrochloric acid that can be added or generated *in situ* by the addition of acetylchloride to the alcohol solvent used gives selective esterification at C-3 to produce (1). IA-3,4-diester (IIA) can be prepared from C-3 monoesters (1) by stirring a C-3 monoester (1) with a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and an appropriate alkyl halide of formula Z²-X, wherein X is a halide such as -Cl, -Br, or -I and Z² is defined above, in a solvent such as benzene, tetrahydrofuran (THF) or acetonitrile. This reaction condition also produces the C-3,C-5-diester and the C-3,C-4,C-5-triesters of IA which can be separated by

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chromatographic methods such as preparative thin layer chromatography on silica gel using solvents such as methylene chloride and acetone with small amounts of acetic acid added (a typical ratio would be 88/8/4 CH₂Cl₂/acetone/acetic acid by volume) or by
5 preparative high pressure liquid chromatography on reverse-phase packing such as ZORBAX RX C8 eluting with a gradient solvent system beginning with acetonitrile/water (1:1 with 0.005% trifluoroacetic acid) and increasing eluting power to 100% acetonitrile (with 0.005% trifluoroacetic acid). In this reaction, using one equivalent of base to
10 substrate ratio mainly gives the C-3,C-4-diesters, while a base to substrate ratio of two or more gives mainly the C-3,C-5-diesters or C-3,C-4,C-5-triesters as the major product.

SCHEME B:

15 When the C-3 monoesterification in Scheme A is carried out in benzyl alcohol, the C-3 benzyl ester (2) formed can be used as a C-3 protecting group. This allows modification of the C-4 and C-5 carboxyl groups to produce (3) by forming esters in these positions with an isourea reagent such as O-t-butyl-N,N'-diisopropyl-isourea.
20 [Mathias, L. J., Synthesis, 561-576 (1979)]. IA-4,5-di-t-butyl diester (4) can be prepared from IA-3-benzyl-4,5-di-t-butyl ester (3) by removing the benzyl group by hydrogenolysis with Pd/C and hydrogen gas or transfer hydrogenolysis with Pd/C and methyl cyclohexadiene. IA-4,5-di-t-butyl diester (4) can be modified at the C-3 position by
25 several procedures. For example, IA-4,5-di-t-butyl diester (4) may be treated with N-methyl morpholine followed by isobutylchloroformate to form a mixed anhydride which reacts well with various alcohols to form the corresponding IA-3-Z¹-4,5-di-t-butyl triesters (5). IA-4,5-di-t-butyl diester (4) may also be treated with coupling reagents such as
30 carbonyl diimidazole, thionyl chloride, benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) or any of the other standard coupling reagents known to those skilled in the art, such as dicyclohexylcarbodiimide (DCC) or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinolone (EEDQ), followed by an alcohol

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to form esters (5). Also IA-4,5-di-t-butyl diester (4) can be converted to the triester (5) by stirring with an Z¹O-N,N'-dialkyl-isourea in a solution such as toluene, benzene, acetonitrile, tetrahydrofuran (THF) and/or dimethoxyethane (DME). [Mathias, L. J., Synthesis, 561-576 (1979)]. The C-4,C-5-di-t-butyl ester groups may be removed later by stirring the triester (5) formed with trifluoroacetic acid (TFA) in methylene chloride to form (1). The C-3 monoesters (1) thus produced may be transformed into the C-3,C-4-diester (IIA) as described in Scheme A.

SCHEME C:

As an alternative to the method of Scheme B, the triester (5) can be selectively saponified at the C-4 position by action of certain Lewis acids such as thionyl chloride, tin(IV) chloride or hydrogen fluoride. A catalytic amount of tin(IV) chloride is used for the saponification, e.g. between 0.05 to 0.5 equivalents per one equivalent of triester (5), with stirring at room temperature for about one to twenty hours; 0.05 equivalents of tin(IV) chloride with stirring for 18 to 20 hours is preferred. An excess of thionyl chloride is used to saponify the triester (5), e.g., from about 40 to 60 equivalents of thionyl chloride per one equivalent of (5), and the reaction is stirred for about 3 to 4 days at room temperature. When hydrogen fluoride is used in this step, a large excess of hydrogen fluoride, e.g. about 350 to 400 equivalents, is used per one equivalent of (5), and the reaction is stirred for about 8 hours to obtain the diester (6). This provides a C-3,C-5 diester (6) that can be esterified at the 4-carboxylic acid to form the IA-3-Z¹-4-Z²-5-t-butyl triester (7) by treatment with one equivalent each of DBU and an alkyl halide per equivalent of diester (6), as described in Scheme A. The C-3,C-5 diester (6) may also be esterified at the 4-carboxylic acid by using the procedures described in Scheme B for producing the triester (5) from the C-4,C-5-di-t-butyl diester (4). Such esterification procedures include treatment of (6) with one equivalent each of N-methyl morpholine and isobutylchloroformate to form a mixed anhydride followed by treatment with from one to five

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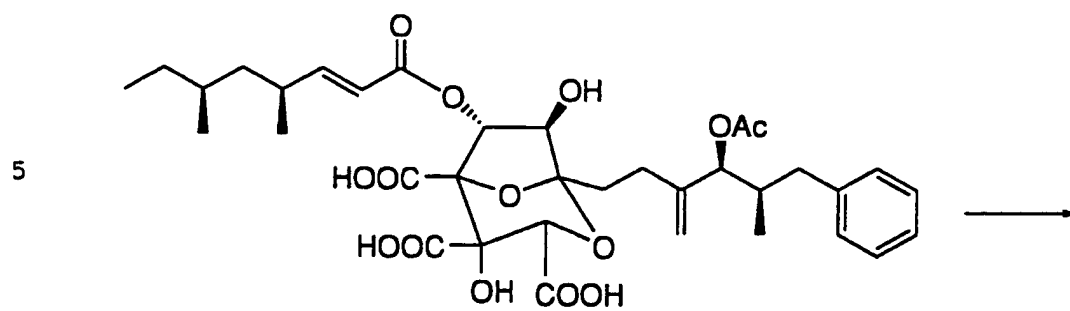
equivalents of an alcohol of formula Z²-OH per equivalent of (6); treatment of (6) with one equivalent of a coupling reagent and one equivalent of the alcohol Z²-OH per equivalent of (6); or treatment of (6) with one to three equivalents of a Z²O-N,N'-dialkyl-isourea per equivalent of (6).

5 The triester (7) may be purified by flash chromatography on silica gel using solvents such as ethyl acetate and methylene chloride. The purified triester (7) may be deprotected by stirring with trifluoroacetic acid (TFA) in methylene chloride to give the compounds of this invention (IIA). The triester (5) can be made via the route
10 shown in Scheme B, or alternatively it can be prepared by reacting compound (1) with t-butyl-O-N,N'-diisopropylisourea. Compound (1) is prepared via the method shown in Scheme A.

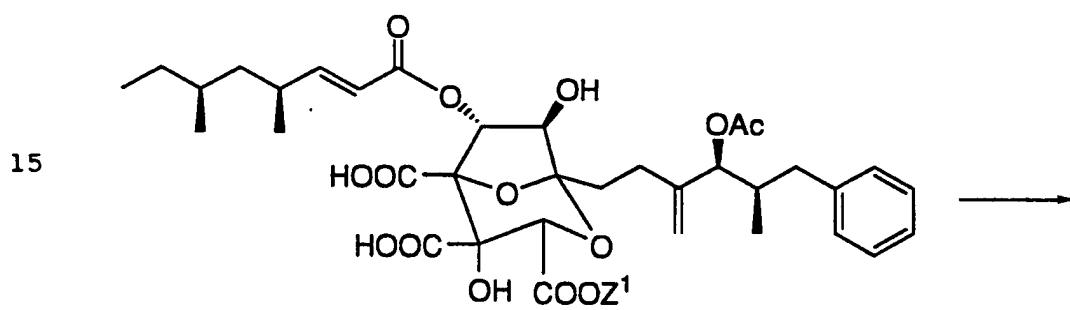
 The present invention is also directed to a method of
15 treating hypercholesterolemia which comprises the administration to a subject in need of such treatment a nontoxic therapeutically effective amount of a compound represented by structural formula (I) and pharmaceutically acceptable salts thereof. Specifically, the compounds of this invention are useful as antihypercholesterolemic agents for the treatment of arteriosclerosis, hyperlipidemia, familial hypercholesterolemia and the like diseases. They may be administered orally or
20 parenterally in the form of a capsule, a tablet, an injectable preparation or the like. It is usually desirable to use the oral route. Active metabolites of the instant compounds are contemplated within the scope of the invention. Doses may be varied, depending on the age, severity,
25 body weight and other conditions of human patients, but daily dosage for adults is within a range of from about 20 mg to 2000 mg (preferably 20 to 100 mg) which may be given in two to four divided doses. Higher doses may be favorably employed as required.

30 The present invention is also directed to a method of inhibiting squalene synthase which comprises the administration to a subject in need of such treatment of a nontoxic therapeutically effective amount of compound represented by structural formula (I) and pharmaceutically acceptable salts thereof. Specifically, the compounds

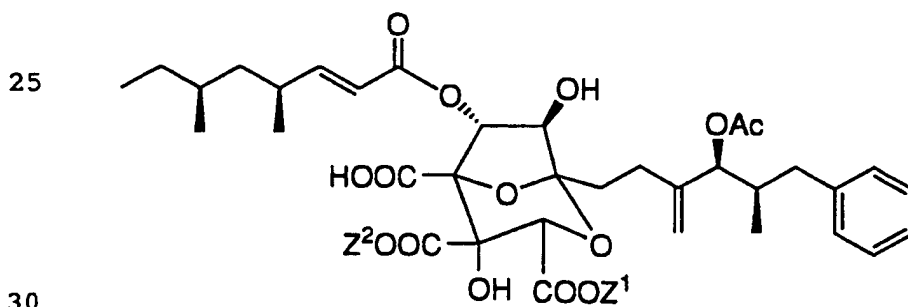
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SCHEME A

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IA

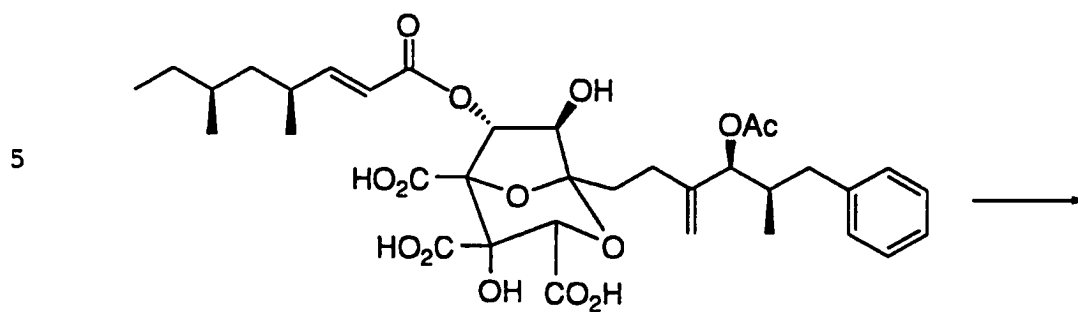
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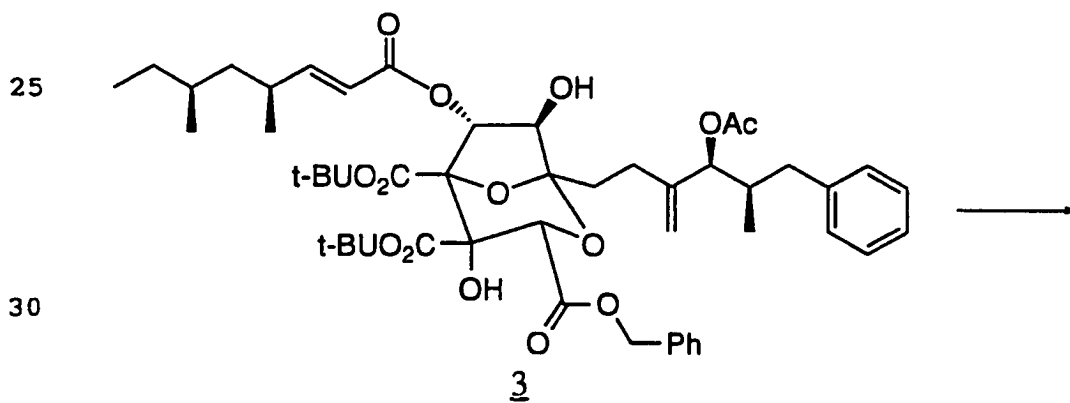
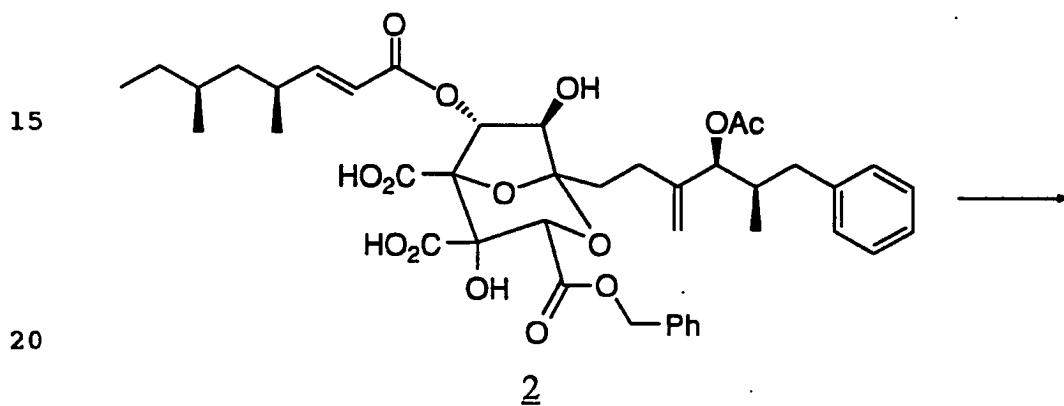
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IIA

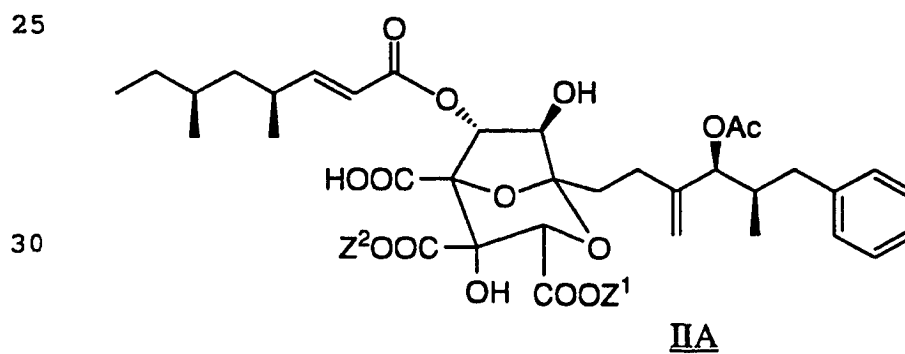
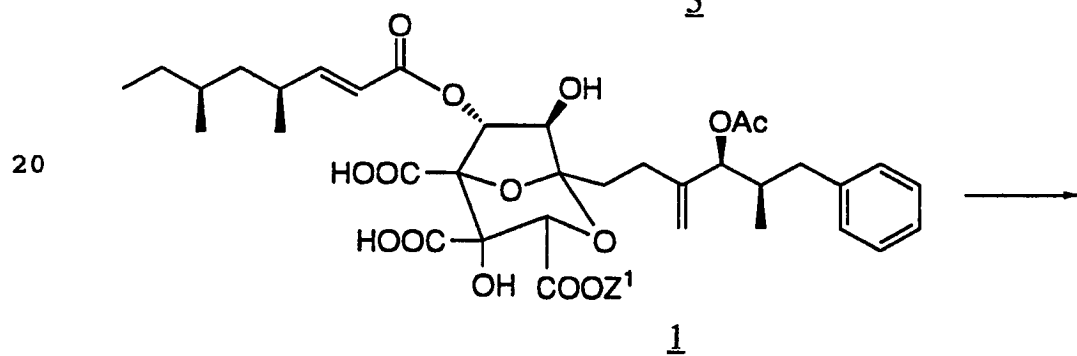
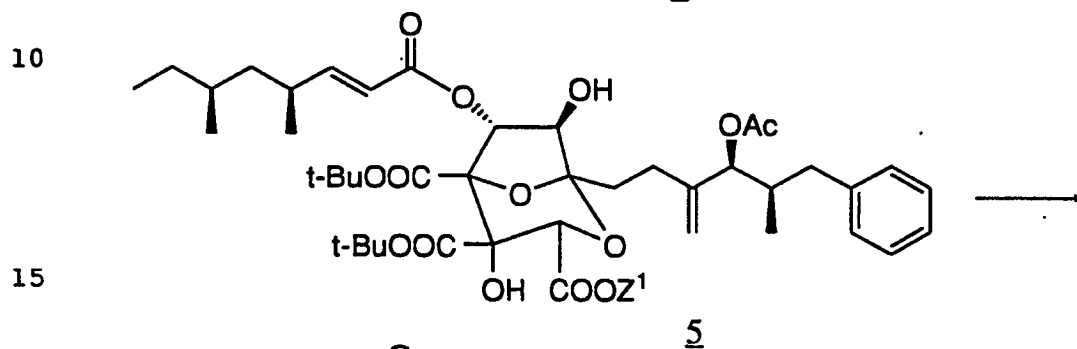
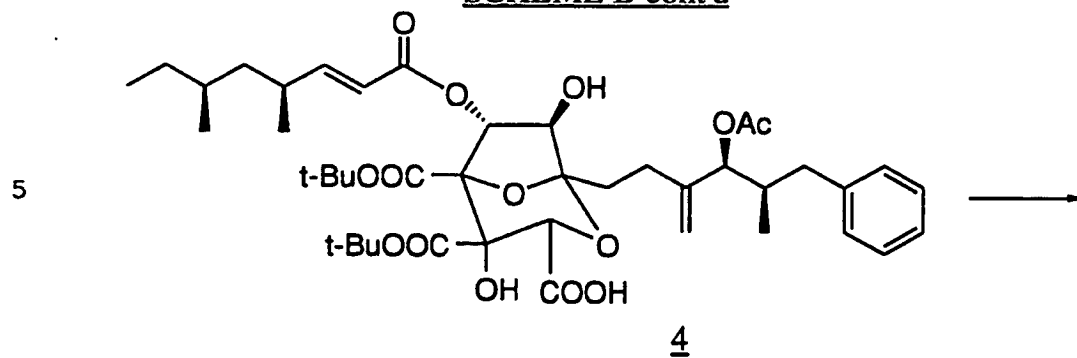
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SCHEME B

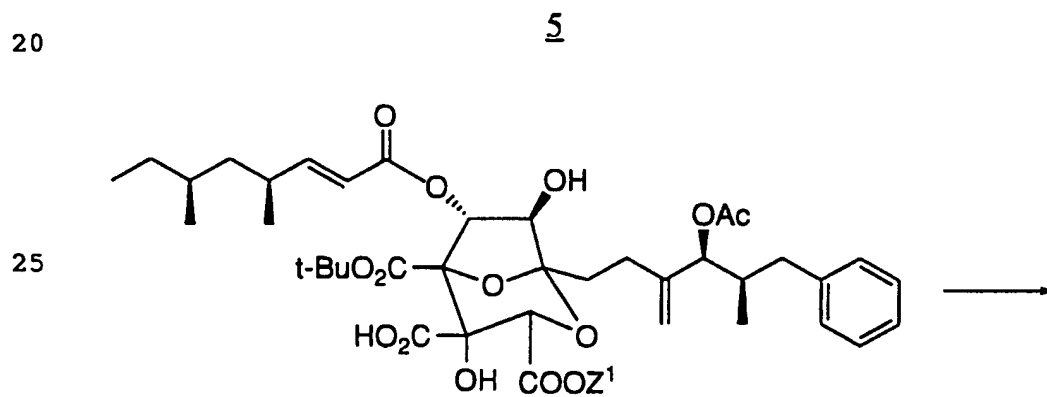
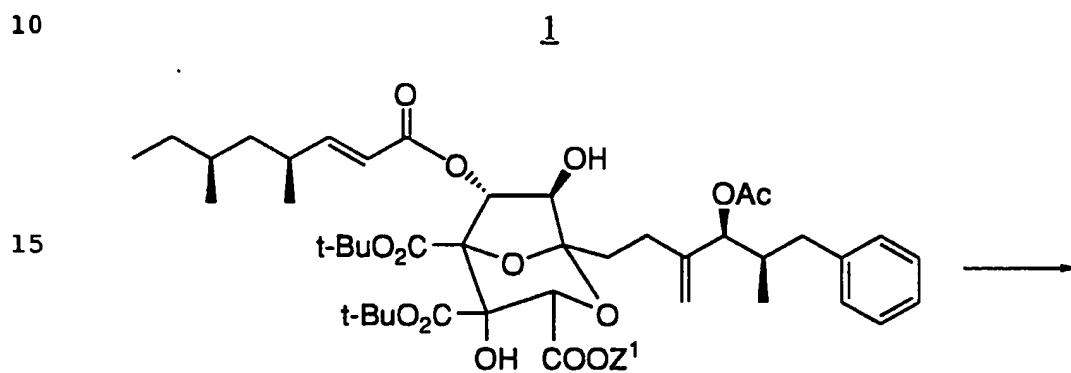
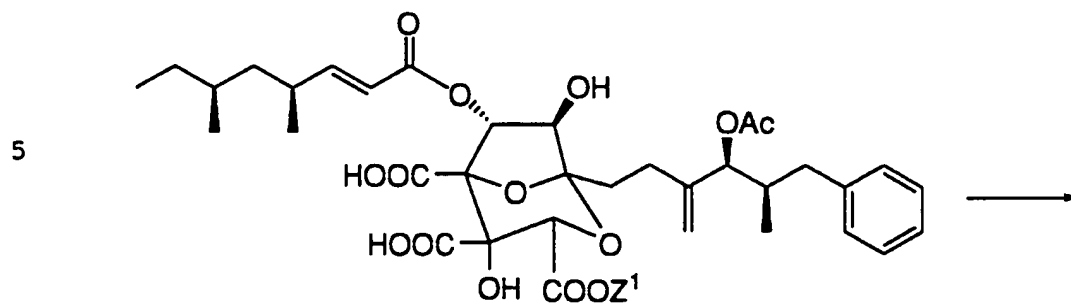
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1A

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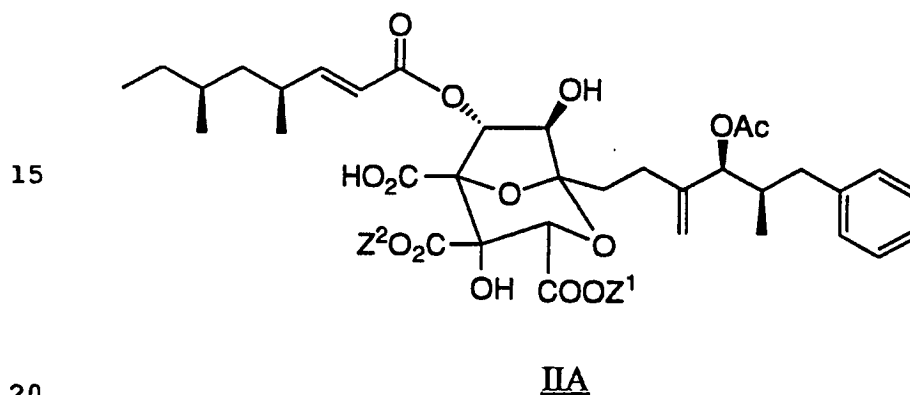
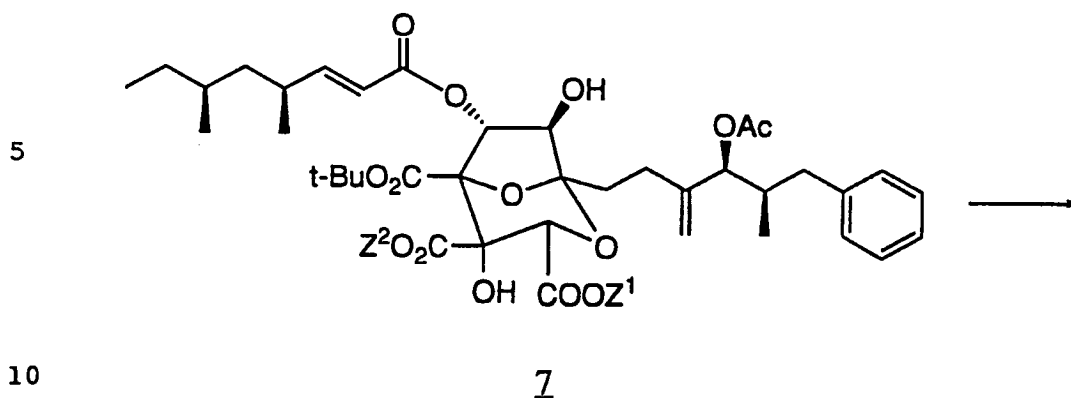
SCHEME B cont'd

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SCHEME C

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- 15 -

SCHEME C cont'd

20 of this invention are useful in treating disease conditions such as, but not limited to, hypercholesterolemia which result from the action of the enzyme squalene synthase. They may be administered orally or parenterally in the form of a capsule, a tablet, an injectable preparation or the like. It is usually desirable to use the oral route. Active

25 metabolites of the instant compounds are contemplated within the scope of the invention. Doses may be varied, depending on the age, severity, body weight and other conditions of human patients, but daily dosage for adults is within a range of from about 20 mg to 2000 mg

30 (preferably 20 to 100 mg) which may be given in two to four divided doses. Higher doses may be favorably employed as required.

The pharmaceutically acceptable salts of the compounds of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from

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bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline, N-N'-dibenzylethylen-diamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide.

5 The compounds of this invention may also be administered in combination with other cholesterol lowering agents such as those which inhibit an enzymatic pathway in the biosynthesis of cholesterol. Example of such agents would include, but are not limited to, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, and squalene
10 epoxidase inhibitors. Illustrative of such inhibitors are lovastatin, simvastatin, pravastatin and fluvastatin. Examples of HMG-CoA synthase inhibitors are: the beta-lactone derivatives disclosed in U.S. Patent Nos. 4,806,564, 4,816,477, 4,847,271, and 4,751,237; the beta-lactam derivatives disclosed in U.S. 4,983,597 and the substituted
15 oxacyclopropane analogues disclosed in European Patent Publication EP O 411 703. Illustrative examples of squalene epoxidase inhibitors are disclosed in European Patent Publication EP O 318 860 and in Japanese Patent Publication JO2 169-571A. LDL-receptor gene inducer molecules are disclosed in U.S. Patent Application Serial No.
20 07/670,640 filed March 18, 1991. Other cholesterol lowering agents that may be administered include niacin, probucol, and the fibric acids, clofibrate and gemfibrozil. Representative of such combinations are those containing about 10-400 mg of a compound of formula (I) in combination with about 20-100 mg of an HMG-CoA reductase inhibitor,
25 20-200 mg of a HMG-CoA synthase inhibitor, or 2-200 mg of a squalene epoxidase inhibitor, or up to 1000 mg of probucol, up to 2 g of clofibrate, 2 to 8 g of niacin, and 800 to 1500 mg gemfibrozil or 20 to 300 mg of an LDL-receptor gene inducer.

30 The compounds of this invention may also be coadministered with pharmaceutically acceptable nontoxic cationic polymers capable of binding bile acids in a non-reabsorbable form in the gastrointestinal tract. Examples of such polymers include cholestyramine, colestipol and poly[methyl-(3-trimethylaminopropyl)-

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imino-trimethylene dihalide]. The relative amounts of the compounds of this invention and these polymers is between 1:100 and 1:15,000.

The usefulness of the compounds of this invention as cholesterol lowering agents is shown by the following assay.

5

Oral Mouse Assay

The compound to be tested is dissolved in 5% EMULPHOR® in 0.9% NaCl at a concentration of 24 mg/kg. The solution of the test compound is given by gavage to each mouse in a dose volume that does not exceed 0.15 ml per mouse. Six mice per group are dosed this way. After dosing of the animals, a 30 minute incubation period is allowed to elapse, and then each animal receives subcutaneously a dose of the radiolabelled tracer tritiated mevalonolactone, 0.5 microcuries, in 25 µl of saline. The tracer used is incorporated into cholesterol and the incorporation is used as a measure of *in vivo* cholesterol synthesis. After dosing with the tracer, another 30 minutes is allowed to elapse and then the animals are sacrificed. Upon sacrifice, each liver is removed and saponified in a solution of 40% KOH/ethyl alcohol overnight at 60°C. Next, the liver/40% KOH/ethyl alcohol mixture is extracted with petroleum ether (2 x 10ml) to remove the non-saponifiables, then one half of the organic layer is counted in a liquid scintillation counter. The numbers (DPMs) observed are expressed as a percentage of the control value to obtain percent inhibition of cholesterol synthesis. The control used is the vehicle (EMULPHOR® and saline).

25

Depending on the results obtained using 24 mg/kg of the compound being tested, the procedure is repeated using 12 mg/kg, 6 mg/kg, 2 mg/kg and 0.67 mg/kg, to obtain sufficient results to calculate the ED50. Representative compounds of this invention tested in this assay demonstrated ED50's of less than 8 mpk.

30

The following Examples illustrate the preparation of the compounds of formula (I) and their incorporation into pharmaceutical compositions and as such are not to be considered as limiting the invention set forth in the claims appended hereto. The word "hour(s)"

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may be abbreviated herein as "hr(s)". The number-letter designations given in parenthesis after compound names in the Examples (e.g., 1a, 1b, 1c, 2a, etc.) correspond to the compounds depicted in Tables 1 and 2, above.

5

EXAMPLE 1

Preparation of IA-3-ethyl-4-pivaloyloxymethyl diester (1b)

Step 1: Preparation of IA-3-ethyl ester (Compound 1 in Scheme A wherein Z¹ is ethyl)

10

A mixture of acetyl chloride (0.15 ml) and absolute ethanol (4 ml) was stirred for 1 hr at room temperature after which time IA was added (500 mg). The resulting mixture was stirred for 15 hrs at room temperature. The solution was concentrated *in vacuo*. One third of the crude product was purified by preparative high pressure liquid chromatography (HPLC) to afford the title compound as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.13-7.27 (m, 5H), 6.81-6.87 (dd, 1H), 6.30 (s, 1H), 5.78 (d, 1H), 5.28 (s, 1H), 5.07 (d, 1H), 5.06 (s, 1H), 5.01 (s, 1H), 4.17-4.22 (m, 2H), 4.03 (s, 1H), 2.65-2.70 (dd, 1H), 2.33-2.45 (m, 4H), 2.22-2.24 (m, 1H), 2.09 (s, 3H), 1.98-2.04 (m, 2H), 1.23-1.42 (t+m, 6H), 1.11-1.15 (m, 2H), 1.02 (d, 3H), 0.84-0.87 (m, 9H).

15

20

Step 2: Preparation of IA-3-ethyl-4-pivaloyloxymethyl diester

25

To a solution of the product from Step 1 (72 mg, 0.10 mmol) in 5 ml of benzene was added DBU (0.016 ml, 0.11 mmol) and chloromethyl pivalate (0.022 ml, 0.15 mmol). The mixture was stirred for 60 hrs at 45°C. The solution was concentrated *in vacuo* and the residue was purified by preparative TLC (thin layer chromatography) then by preparative HPLC to give the title compound.

30

¹H NMR (400 MHz, CD₃OD) δ 7.16- 7.26 (m, 5H), 6.80-6.87 (dd, 1H), 6.11 (s, 1H), 5.89-5.90 (d, 1H), 5.83-5.84 (d, 1H), 5.77-5.81 (d, 1H), 5.21 (s, 1H), 5.07 (d, 1H), 5.01 (s, 1H), 4.95 (s, 1H), 4.14-4.24 (m, 2H), 4.02 (s, 1H), 2.68 (dd, 1H), 2.39-2.48 (m 3H), 2.28-2.36 (m 1H), 2.18-2.26 (m, 1H), 2.09 (s, 3H), 1.98-2.03 (m, 2H), 1.20-1.42 (s+t+m,

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15H), 1.10-1.16 (m, 2H), 1.02 (d, 3H), 0.85-0.88 (m, 9H). MS, FAB(-) m/e 831 (m⁺ -1).

By the method described in Scheme A and Example 1, the following compounds described in Examples 2-17 were prepared.

EXAMPLE 2

IA-3-ethyl-4-(1-pivaloyloxy)ethyl diester (1h)

¹H NMR (400 MHz, CD₃OD) δ 6.91-7.02 (q, 1H), 6.76-6.88 + 6.78-6.90 (dd+dd, 1H, 3:1), 6.12+6.29 (d+d, 1H, 3:1), 5.22+5.16 (s+s, 1H, 3:1), 3.99+4.03 (d+d, 1H, 3:1), 1.53 (d, 3H). MS, FAB(-) m/e 845 (m⁺-1).

EXAMPLE 3

IA-3-ethyl-4-(1-ethoxycarbonyloxy)ethyl diester (1f)

¹H NMR (400 MHz, CD₃OD) δ 6.81-6.87 (m, 2H), 6.12+6.24 (d+d, 1H, 4:1), 5.22+5.18 (s+s, 1H, 4:1), 4.01+4.05 (d+d, 1H, 4:1), 1.57+1.62 (d+d, 3H, 4:1). MS, FAB(-) m/e 833 (m⁺-1).

EXAMPLE 4

IA-3-ethyl-4-(3-phthalidyl) diester (1j)

¹H NMR (400 MHz, CD₃OD) δ 7.91 (d, 1H), 7.79 (s, 2H), 7.70-7.75 (m, 1H), 7.55 (s, 1H), 7.11-7.26 (m, 5H), 6.84-6.90 (dd, 1H), 6.26 (d, 1H), 5.80 (d, 1H), 5.31 (s, 1H), 5.06 (d, 1H), 5.00 (s, 1H), 4.96 (s, 1H), 4.23-4.32 (m, 2H), 4.06 (d, 1H), 2.64-2.70 (dd, 1H), 2.38-2.50 (m, 3H), 2.28-2.37 (m, 1H), 2.17-2.27 (m, 1H), 2.09 (s, 3H), 2.00-2.04 (m, 2H), 1.24-1.42 (t+m, 6H), 1.08-1.18 (m, 2H), 1.01 (d, 3H), 0.81-0.86 (m, 9H). MS, FAB(-) m/e 849 (m⁺-1).

EXAMPLE 5

IA-3-ethyl-4-(5'-methyl-2'-oxo-1',3'-dioxolen-4'-yl)-methyl diester (11')

¹H NMR (400 MHz, CD₃OD) δ 7.11-7.26 (m, 5H), 6.83-6.89 (dd, 1H), 6.14 (d, 1H), 5.85 (d, 1H), 5.17 (s, 1H), 5.00-5.10 (m,

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5H), 4.12-4.20 (q, 2H), 4.01 (d, 1H), 2.67-2.72 (dd, 1H), 2.30-2.52 (m, 4H), 2.18-2.28 (m, 1H), 2.18 (s, 3H), 2.09 (s, 3H), 2.00-2.07 (m, 2H), 1.26-1.42 (m, 3H), 1.20 (t, 3H), 1.08-1.17 (m, 2H), 1.01 (d, 3H), 0.84-0.87 (m, 9H). MS, FAB(-) m/e 829 (m⁺-1).

5

EXAMPLE 6

IA-3-methyl ester

¹H NMR (400 MHz, CD₃OD) δ 7.29-7.09 (m, 5H), 6.85 (dd, J=15.6, 8.5 Hz, 1H), 6.31 (d, J=1.8 Hz, 1H), 5.80 (d, J=15.6 Hz, 1H), 5.31 (s, 1H), 5.09 (d, J=4.9 Hz, 1H), 5.03 (s, 1H), 4.98 (s, 1H), 4.02 (d, J=1.7 Hz, 1H), 3.72 (s, 3H), 2.70 (m, 1H), 2.45 (m, 3H), 2.36-2.21 (m, 3H), 2.05 (s, 3H), 1.45-1.26 (m, 6H), 1.19-1.10 (m, 3H), 1.05 (d, J=6.4 Hz, 3H), 0.91-0.82 (m, 10H), MS data (FAB) 685 (M+Na)⁺.

10

EXAMPLE 7

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IA-3-methyl-4-pivaloyloxymethyl diester (1a)

¹H NMR (400 MHz, CD₃OD) δ 7.13-7.27 (m, 5H), 6.82-6.88 (dd, 1H), 6.12 (s, 1H), 5.90-5.91 (d, 1H), 5.79-5.83 (d, 2H), 5.23 (s, 1H), 5.06 (d, 1H), 5.03 (s, 1H), 4.96 (s, 1H), 4.02 (s, 1H), 3.72 (s, 3H), 2.66 (dd, 1H), 2.26-2.38 (m, 1H), 2.19-2.26 (m, 1H), 2.09 (s, 3H), 1.91-2.04 (m, 2H), 1.29-1.35 (m, 3H), 1.22 (s, 9H), 1.10-1.17 (m, 2H), 1.01 (d, 3H), 0.84-0.87 (m, 9H). MS, FAB(-) m/e 818.3 (m⁺-1).

20

EXAMPLE 8

IA-3-isopropyl ester

¹H NMR (200 MHz, CD₃OD) δ 7.30-7.10 (m, 5H), 6.86 (dd, J=8, 16 Hz, 1H), 6.31 (d, J=1.7 Hz, 1H), 5.80 (d, J=16 Hz, 1H), 5.26 (s, 1H), 5.10 (d, J=4.6 Hz, 1H), 5.04 and 5.00 (ea s, ea 1H), 4.11 (t, J=7 Hz, 2H), 4.03 (d, J=1.8 Hz, 1H), 2.68 (m, 1H), 2.52-2.10 (m), 2.10 (s, 3H), 1.40-1.10 (m), 1.24 (d, J=7 Hz, 6H), 1.01 (d, J=7 Hz, 3H), 0.90-0.75 (m).

30

EXAMPLE 9

IA-3-isopropyl-4-pivaloyloxymethyl diester (1e)

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¹H NMR (400 MHz, CD₃OD) δ 7.12-7.27 (m, 5H), 6.80-6.87 (dd, 1H), 6.10 (d, 1H), 5.91 (d, 1H), 5.85 (d, 1H), 5.78 (d, 1H), 5.18 (s, 1H), 5.07 (d, 1H), 4.95-5.00 (2s, 3H), 4.02 (d, 1H), 2.64-2.70 (dd, 1H), 2.40-2.46 (m, 3H), 2.28-2.36 (m, 1H), 2.18-2.26 (m, 1H), 2.09 (s, 3H), 1.98-2.04 (m, 2H), 1.19-1.41 (s+d+m, 18H), 1.09-1.16 (m, 2H), 1.01 (d, 3H), 0.84-0.87 (m, 9H). MS, FAB(-) m/e 845 (m⁺-1).

EXAMPLE 10

IA-3-n-propyl ester

¹H NMR (200 MHz, CD₃OD) δ 7.30-7.10 (m, 5H), 6.84 (dd, J=8, 16 Hz, 1H), 6.31 (d, 1.7 Hz, 1H), 5.80 (d, J=16 Hz, 1H), 5.29 (s, 1H), 5.08 (d, J=4.6 Hz, 1H), 5.03 and 4.97 (ea s, ea 1H), 4.11 (t, J=7 Hz, 2H), 4.04 (d, J=1.8 Hz, 1H), 2.69 (m, 1H), 2.52-2.10 (m), 2.10 (s, 3H), 1.90-1.12 (m), 1.65 (q, J=7 Hz, 2H), 1.44-1.06 (m), 1.01 (d, J=7 Hz, 3H), 0.94 (t, J=7 Hz, 3H), 0.86 (m).

EXAMPLE 11

IA-3-n-propyl-4-pivaloyloxymethyl diester (1c)

¹H NMR (400 MHz, CD₃OD) δ 7.13-7.26 (m, 5H), 6.85 (dd, 1H), 6.09 (d, 1H), 5.78-5.93 (d+dd, 3H), 5.22 (s, 1H), 5.07 (d, 1H), 4.99 (s, 1H), 4.96 (s, 1H), 4.10 (t, 2H), 4.02 (d, 1H), 2.69 (dd, 1H), 2.27-2.50 (m, 4H), 2.17-2.25 (m, 1H), 2.08 (s, 3H), 2.00-2.06 (m, 2H), 1.62-1.70 (m, 2H), 1.26-1.41 (m, 3H), 1.22 (s, 9H), 1.08-1.17 (m, 2H), 1.01 (d, 3H), 0.93 (t, 3H), 0.84-0.86 (m, 9H). MS, FAB(-) m/e 845 (m⁺-1).

EXAMPLE 12

IA-3-n-propyl-4-(1-pivaloyloxy)ethyl diester (1i)

¹H NMR (400 MHz, CD₃OD) δ 6.98+6.93 (q+q, 1H, 3:1), 6.12+6.28 (d+d, 1H, 3:1), 5.24+5.18 (s+s, 1H, 3:1), 4.01+4.04 (d+d, 1H, 3:1), 1.55 (t, 3H). MS, FAB(-) m/e 859 M⁺-1).

EXAMPLE 13

IA-3-n-propyl-4-(1-ethoxycarbonyloxy)ethyl diester (1g)

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^1H NMR (400 MHz, CD_3OD) δ 6.81-6.87 (m, 2H), 6.12+6.24 (d+d, 1H, 5:1), 5.24+5.21 (s+s, 1H, 5:1), 4.15-4.21+4.07-4.12 (m+m, 2H, 5:1), 4.01+4.05 (d+d, 1H, 5:1), 1.56+1.62 (d+d, 3H, 5:1). MS, FAB(-) m/e 847 (M^+-1).

5

EXAMPLE 14IA-3-n-propyl-4-(3-phthalidyl) diester (1k)

^1H NMR (400 MHz, CD_3OD) δ 7.90 (d, 1H), 7.79-7.81 (m, 2H), 7.68-7.73 (m, 1H), 7.52 (s, 1H). MS, FAB(-) m/e 863 (m^+-1).

10

EXAMPLE 15IA-3-n-propyl-4-(5'-methyl-2'-oxo-1',3'-dioxolen-4'-yl)-methyl diester (1m)

^1H NMR (400 MHz, CD_3OD) δ 5.23 (s, 1H), 5.15 (d, 1H), 5.07 (d, 1H), 5.00 (d, 2H), 4.96 (s, 1H). MS, FAB(-) m/e 843 (m^+-1).

15

EXAMPLE 16Step 1: IC-3-ethyl ester

^1H NMR (400 MHz, CD_3OD) δ 4.10-4.21 (m, 2H), 1.18-1.26 (t+m, 5H). MS, FAB(-) m/e 781 (M^+-1).

20

Step 2: IC-3-ethyl-4-pivaloyloxymethyl diester (2a)

^1H NMR (400 MHz, CD_3OD) δ 7.21-7.25 (m, 4H), 7.12-7.16 (m, 6H), 6.07 (d, 1H), 5.83-5.86 (dd, 2H), 5.27-5.42 (m, 2H), 5.17 (s, 1H), 4.14-4.24 (m, 2H), 4.01 (d, 1H), 2.70-2.75 (dd, 1H), 2.53-2.58 (m, 2H), 2.25-2.37 (t+m, 5H), 2.00-2.11 (m, 2H), 2.02 (s, 3H), 1.86-1.91 (m 2H), 1.64-1.74 (m, 2H), 1.53-1.64 (m, 4H), 1.20-1.34 (s+m, 15H), 0.92 (d, 3H), 0.84 (d, 3H). MS, FAB(-) m/e 895 (m^+-1).

25

30

EXAMPLE 17Step 1: IC-3-n-propyl ester

^1H NMR (400 MHz, CD_3OD) δ 4.04 (t, 2H), 1.50-1.68 (m, 8H), 0.86-0.90 (m, 6H). MS, FAB(-) m/e 795 (M^+-1).

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Step 2: IC-3-n-propyl-4-pivaloyloxymethyl diester (2b)

¹H NMR (400 MHz, CD₃OD) δ 7.20-7.25 (m, 4H), 7.12-7.15 (m, 6H), 6.04 (d, 1H), 5.81-5.87 (dd, 2H), 5.26-5.42 (m, 2H), 5.16 (s, 1H), 4.07 (t, 2H), 3.97 (d, 1H), 2.70-2.76 (dd, 1H), 2.55 (td, 2H), 2.26-2.36 (m, 5H), 1.97-2.10 (m, 2H), 2.00 (s, 3H), 1.84-1.89 (m, 2H), 1.52-1.68 (m, 8H), 1.20-1.32 (m, 3H), 1.17 (s, 9H), 0.90-0.94 (m, 6H), 0.84 (d, 3H). MS, FAB(-) m/e 909 (m⁺-1).

The following was prepared according to the method described in Scheme B.

EXAMPLE 18

Preparation of IA-3-allyl-4-pivaloyloxymethyl diester (1d)

Step 1: Preparation of IA-3-benzyl ester

The title compound was prepared by the procedure described in Example 1, Step 1.
¹H NMR (300 MHz, CD₃OD) δ 7.46-7.12 (m, 10H), 6.88 (dd, J=8.9, 18 Hz, 1H), 6.38 (brs, 1H), 5.84 (d, J=15 Hz, 1H), 5.42 (s, 1H), 5.23 (dd, J=13, 51 Hz, 2H), 5.14 (s, 1H), 5.04 & 5.00 (2s, 2H), 4.06 (br s, 1H), 2.71 (m, 1H), 2.54-2.00 (m, 7H), 2.12 (s, 3H), 1.50-1.1 (m, 6H), 1.07 (d, J=6 Hz, 3H), 0.90 (m, 9H); FAB m/e 793 (M+2Li), 799 (M+3Li).

Step 2: Preparation of IA-3-benzyl-4,5-di-t-butyl triester

To a solution of IA-3-benzyl ester (100 mg) in methylene chloride (2 mL) was added O-t-butyl-N, N'-diisopropylisourea (300 mg) and the solution was stirred at 40°C for 2 days. The reaction mixture was then cooled to room temperature, concentration *in vacuo* and filtered through silica eluting with ethyl acetate:hexane, 1:4 to yield the title compound.

¹H NMR (400 MHz, CDCl₃) δ 7.35-7.08 (m, 10H), 6.89 (dd, J=16, 8.4 Hz, 1H), 5.97 (d, J=1 Hz, 1H), 5.75 (d, J=16 Hz, 1H), 5.24 (s, 1H), 5.16 (dd, J=12 Hz, 64 Hz, 2H), 5.06 (br s, 1H), 4.94 (br s, 2H), 4.00 (br s, 1H), 2.96 (d, J=2 Hz, 1H), 2.66 (m, 1H), 2.5--2.2 (m, 5H), 2.15-2.00

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(m, 4H), 2.05 (s, 3H), 1.39 (s, 9H), 1.37 (s, 9H), 1.40-1.05 (m, 6H), 1.02 (d, J=6 Hz, 3H), 0.86-0.76 (m, 9H).

Step 3: Preparation of IA-4,5-di-t-butyl-diester

5 To a solution of IA-3-benzyl-4,5-di-t-butyl triester (100 mg) in methanol (4 mL) was added 1-methyl-1,4-cyclohexadiene (200 μ L) and Pd/C (50 mg). The reaction mixture was stirred at 30-35°C for 1.5 hr and filtered over celite. The filtrate was evaporated *in vacuo* to give the title compound.

10 ¹H NMR (400 MHz, CD₃OD) δ 7.30-7.10 (m, 5H), 6.89 (dd, J=8.16 Hz, 1H), 6.43 (d, J=1 Hz, 1H), 5.82 (d, J=16 Hz, 1H), 5.06 (d, J=5 Hz, 1H), 5.04 (s, 1H), 5.01 & 4.96 (each s, each 1H), 4.07 (s, 1H), 2.69 (m, 1H), 2.5-2.20 (m, 6H), 2.10 (s, 3H), 1.60 (s, 9H), 1.42 (s, 9H), 1.65-1.05 (m, 6H), 1.03 (d, J=8.1 Hz, 3H), 0.88 (m, 10H).

15 **Step 4: Preparation of IA-3-allyl-4,5-di-t-butyl triester**

To the IA-4,5-di-t-butyl diester (200 mg, 0.25 mmol) in benzene (3 ml) was added DBU (0.074 ml, 0.5 mmol) and allyl bromide (0.043 ml, 0.5 mmol). The resulting mixture was stirred overnight at room temperature. The solution was filtered and concentrated. The product was purified by preparative TLC (25% EtOAc in hexane) to give 88 mg of the title compound.

20 ¹H NMR (200 MHz, CDCl₃) δ 7.04-7.24 (m, 5H), 6.80-6.92 (dd, 1H), 5.95 (dd, 1H), 5.68-5.90 (d+m, 2H), 5.10-5.29 (m, 2H), 5.17 (s, 1H), 5.04 (d, 1H), 4.90 (s, 2H), 4.49-4.68 (m, 2H), 3.96-4.02 (s+broad s, 2H), 3.03 (d, 1H), 2.60-2.70 (dd, 1H), 2.25-2.46 (m, 5H), 1.98-2.12 (s+m, 5H), 1.48 (s, 9H), 1.36 (s, 9H), 1.02-1.36 (m, 5H), 0.96 (d, 3H), 0.72-0.80 (m, 9H). MS, FAB(-) m/e 801 (m⁺-1-C₃H₄).

25 **Step 5: Preparation of IA-3-allyl ester**

30 To the product from Step 1 (160 mg) in CH₂Cl₂ (10 ml) was added TFA (0.9 ml). The mixture was stirred overnight at room temperature. The solution was concentrated. The residue was flashed with 2 x 2 ml of toluene to get rid of the trace amount of TFA. The

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product was purified by preparative reverse phase HPLC to afford 134 mg of the title compound.

¹H NMR (200 HMz, CD₃OD) δ 7.10-7.26 (m, 5H), 6.76-6.88 (dd, 1H), 6.28 (d, 1H), 5.72-5.93 (d+m, 2H), 5.15-5.37 (s+m, 3H), 5.04 (d, 1H), 4.98 (s, 1H), 4.93 (s, 1H), 4.58-4.65 (m, 2H), 3.99 (d, 1H), 2.58-2.70 (dd, 1H), 2.12-2.48 (m, 5H), 1.92-2.08 (s+m, 5H), 1.02-1.36 (m, 5H), 0.96 (d, 3H), 0.77-0.84 (m, 9H).

Step 6: Preparation of IA-3-allyl-4-pivaloyloxymethyl diester

The title compound was prepared from the product of Step 2, above, according to the procedure described in Example 1, Step 2. ¹H NMR (200 MHz, CD₃OD) δ 7.10-7.23 (m, 5H), 6.76-6.88 (dd, 1H), 6.11 (dd, 1H), 5.72-5.94 (d+dd+m, 4H), 5.17-5.36 (s+m, 3H), 5.03 (d, 1H), 4.98 (s, 1H), 4.95 (s, 1H), 4.58-4.64 (m, 2H), 3.98 (d, 1H), 2.58-2.68 (dd, 1H), 2.11-2.33 (m, 5H), 2.09 (s, 3H), 1.92-2.10 (m, 2H), 1.06-1.41 (s+m, 14H), 0.97 (d, 3H), 0.76-0.85 (m, 9H). MS, FAB(-) m/e 843 (m⁺-1).

EXAMPLE 19

As a specific embodiment of an oral composition of a compound of this invention, 20 mg of the compound 1b from Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

EXAMPLE 20

Preparation of an Ammonium Salt

A 0.1 mmol sample of the free acid of a compound of formula (I) is dissolved in 10 mL of ethyl acetate. The resulting solution is saturated with gaseous ammonia upon which the ammonium salt precipitates from solution.

EXAMPLE 21

Preparation of a Potassium Salt

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A solution of 0.1 mmol of the free acid of a compound of formula (I) in 10 mL of methanol is treated with an aqueous or methanolic solution containing 0.1 mmol of potassium hydroxide. Evaporation of the solvent affords the potassium salt.

5 In a similar fashion the sodium and lithium salts can be formed.

EXAMPLE 22

Preparation of a Calcium Salt

10 A solution of 0.1 mmol of the free acid of a compound of formula (I) in 20 mL 6:4 methanol/water is treated with an aqueous solution of 0.1 mmol of calcium hydroxide. The solvents are evaporated to give the corresponding calcium salt.

EXAMPLE 23

Preparation of an Ethylenediamine Salt

15 A solution of 0.1 mmol of the free acid of a compound of formula (I) in 10 mL 6:4 methanol is treated with 0.1 mmol of ethylenediamine. Evaporation of the solvent affords the ethylenediamine salt.

20

EXAMPLE 24

Preparation of a Tris(hydroxymethyl)aminomethane Salt

25 To a solution of 0.1 mmol of the free acid of a compound of formula (I) in 10 mL of methanol is added from 0.1 to 0.3 mmol of tris(hydroxymethyl)-aminomethane dissolved in 10 mL of methanol. Evaporation of the solvent gives a corresponding salt form of the exact composition of which is determined by the molar ratio of amine added. Similarly prepared are the salts of L-ornithine, L-lysine, and N-methylglucamine.

30

EXAMPLE 25

Preparation of an L-arginine Salt

- 27 -

A solution of 0.1 mmol of the free acid of a compound of formula (I) in 10 mL of 6:4 methanol/water is treated with an aqueous solution of 0.1 to 0.3 mmol of L-arginine. Evaporation of the solvent affords the title salt, the exact composition of which is determined by the molar ratio of amino acid to the free acid of formula (I) used.

Similarly prepared are the salts of L-ornithine, L-lysine and N-methylglucamine.

The following was prepared according to the method described in Scheme C.

EXAMPLE 26

Preparation of IA-3-n-propyl-4-pivaloyloxymethyl diester (1c)

Step 1: Preparation of IA-3-n-propyl-4,5-di-butyl triester

A solution of 1-propanol (7.5 ml) and acetyl chloride (0.18 ml) was stirred for 1 hr at room temperature to which was added IA (2.5 g). The resulting mixture was stirred overnight at room temperature. The solution was concentrated. The residue was dissolved in 20 ml of CH₂Cl₂ and added O-t-butyl-N,N'-diisopropylisourea (8 g) was added. After stirring overnight at room temperature, the solution was filtered and concentrated. The residue was purified by flash chromatography on silica gel (25% EtOAc in hexane) to yield the title compound.

¹H NMR (200 MHz, CDCl₃) δ 7.07-7.22 (m, 5H), 6.80-6.92 (dd, 1H), 5.97 (d, 1H), 6.72 (d, 1H), 5.17 (s, 1H), 5.05 (d, 1H), 4.91 (s, 2H), 3.97-4.12 (d+m, 4H), 3.18 (br s, 1H), 2.60-2.69 (dd, 1H), 2.25-2.45 (m, 4H), 1.98-2.12 (s+m, 6H), 1.48-1.67 (s+m, 11H), 1.42 (s, 9H), 1.03-1.31 (m, 5H), 0.98 (d, 3H), 0.72-0.86 (m, 12H).

Step 2: Preparation of IA-3-n-propyl-5-t-butyl diester

To the product of Step 1, above, (1g) in THF (20 ml) was added thionyl chloride (3.45 ml). After stirring overnight at room temperature, the solution was concentrated. The residue was dissolved in di-ethyl ether (40 ml) and poured into 50 ml of saturated NaHCO₃ solution. The ether phase was separated, dried and concentrated. The

- 28 -

residue was purified by preparative TLC (8% MeOH in CH₂Cl₂) to afford the title compound.

¹H NMR (200 MHz, CD₃OD) δ 7.10-7.27 (m, 5H), 6.69-6.81 (dd, 1H), 6.56 (br s, 1H), 5.78 (d, 1H), 5.34 (s, 1H), 5.05 (d, 1H), 4.96 (s, 1H), 4.92 (s, 1H), 4.04 (t, 2H), 3.95 (d, 1H), 2.67 (dd, 1H), 2.16-2.52 (m, 5H), 2.04 (s, 3H), 1.86-2.00 (m, 2H), 1.56-1.68 (m, 2H), 1.04-1.40 (s+m, 14H), 0.97 (d, 3H), 0.88 (t, 3H), 0.78-0.84 (m, 9H).

Step 3: Preparation of IA-3-n-propyl-4-pivaloyloxymethyl diester

To the product of Step 2, above, (0.5 g) in CH₃CN (10 ml) was added DBU (0.14 ml) and chloromethyl pivalate (0.14 ml). The mixture was refluxed overnight. The solution was filtered and concentrated. The residue was purified by preparative TLC (25% EtOAc in hexane) to give IA-3-propyl-4-pivaloyloxymethyl-5-t-butyl triester. The product was then dissolved in 10 ml of CH₂Cl₂ and TFA (1.6 ml) was added. The mixture was stirred overnight at room temperature. The solution was concentrated and flashed with 3 x 3ml of toluene. The residue was purified by preparative TLC (8% MeOH in CH₂Cl₂) then by preparative HPLC to yield the title compound.

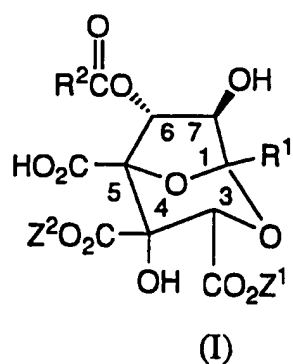
¹H NMR (400 MHz, CD₃OD) δ 7.13-7.26 (m, 5H), 6.85 (dd, 1H), 6.09 (d, 1H), 5.78-5.93 (d+dd, 3H), 5.22 (s, 1H), 5.07 (d, 1H), 4.99 (s, 1H), 4.96 (s, 1H), 4.10 (t, 2H), 4.02 (d, 1H), 2.69 (dd, 1H), 2.27-2.50 (m, 4H), 2.17-2.25 (m, 1H), 2.08 (s, 3H), 2.00-2.06 (m, 2H), 1.62-1.70 (m, 2H), 1.26-1.41 (m, 3H), 1.22 (s, 9H), 1.08-1.17 (m, 2H), 1.01 (d, 3H), 0.93 (t, 3H), 0.84-0.86 (m, 9H). MS, FAB(-) m/e 845 (m⁺-1).

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, or modifications, as come within the scope of the following claims and its equivalents.

- 29 -

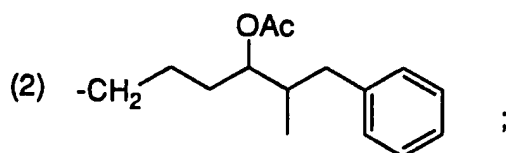
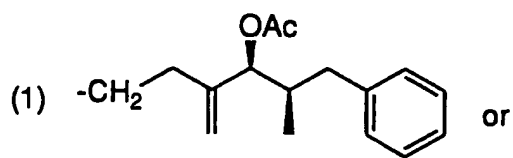
WHAT IS CLAIMED IS:

1. A compound of structural formula (I):

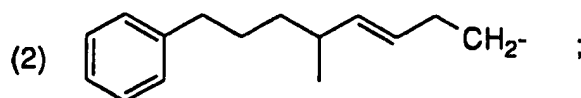


wherein:

R¹ is



25 R² is



Z¹ is C₁-3alkyl or -CH₂-CH=CH₂;

- 30 -

Z² is (1) $\text{-CHR}^3\text{-OC(=O)-(O)}_n\text{-R}^4$

wherein:

R³ is -H or C₁₋₄alkyl,

n is zero or 1, and

R⁴ is

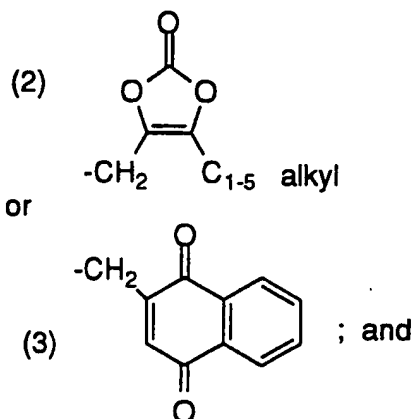
(a) C₁₋₅ alkyl,

(b) phenyl, or

(c) phenyl substituted with X and Y, defined below,

or, when R³ is C₁₋₄ alkyl, R³ and R⁴ are joined together to form a monocyclic or bicyclic ring system,

or, R⁴ is joined together with the carbon to which R³ is attached to form a monocyclic or bicyclic ring system, and R³ represents the bond between R⁴ and the carbon to which R³ is attached,



X and Y are each independently:

(1) hydrogen,

(2) hydroxy,

(3) halogen,

(4) trifluoromethyl,

(5) C₁₋₄alkyl,

(6) C₁₋₄alkyl-O-,

(7) C₁₋₄alkyl-C(O)-O-,

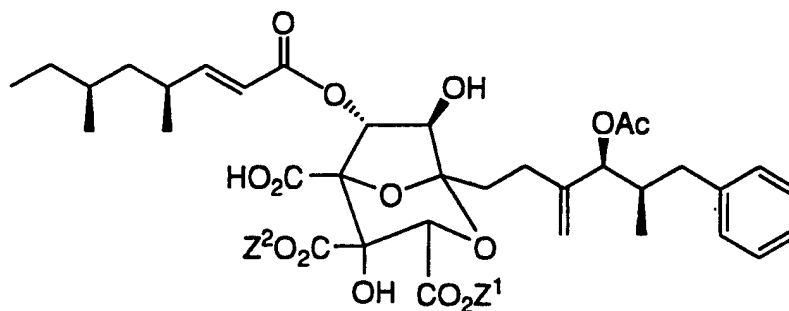
(8) -CO₂C₁₋₄alkyl,

(10) -CO₂H, or

- 31 -

(11) nitro;
or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 having structural formula
(II):



(II)

selected from the group consisting of those wherein:

- (a) Z^1 is CH_3 and Z^2 is $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- (b) Z^1 is $-\text{CH}_2\text{CH}_3$ and Z^2 is $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- (c) Z^1 is $-\text{CH}_2\text{CH}_2\text{CH}_3$ and Z^2 is $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- (d) Z^1 is $-\text{CH}_2\text{-CH=CH}_2$ and Z^2 is $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- (e) Z^1 is $-\text{CH}(\text{CH}_3)_2$ and Z^2 is $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- (f) Z^1 is $-\text{CH}_2\text{CH}_3$ and Z^2 is $-\text{CH}(\text{CH}_3)\text{OC}(=\text{O})\text{OCH}_2\text{CH}_3$;
- (g) Z^1 is $-\text{CH}_2\text{CH}_2\text{CH}_3$ and Z^2 is $-\text{CH}(\text{CH}_3)\text{OC}(=\text{O})\text{OCH}_2\text{CH}_3$;

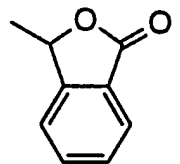
- 32 -

(h) Z¹ is -CH₂CH₃ and Z² is -CH(CH₃)OC(=O)C(CH₃)₃;

(i) Z¹ is -CH₂CH₂CH₃ and Z² is -CH(CH₃)OC(=O)C(CH₃)₃;

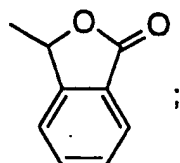
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(j) Z¹ is -CH₂CH₂CH₃ and Z² is



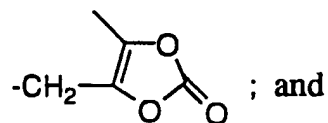
10

(k) Z¹ is -CH₂CH₂CH₃ and Z² is



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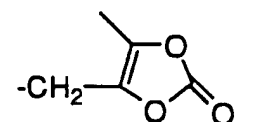
(l') Z¹ is -CH₂CH₂CH₃ and Z² is



; and

20

(m) Z¹ is -CH₂CH₂CH₃ and Z² is

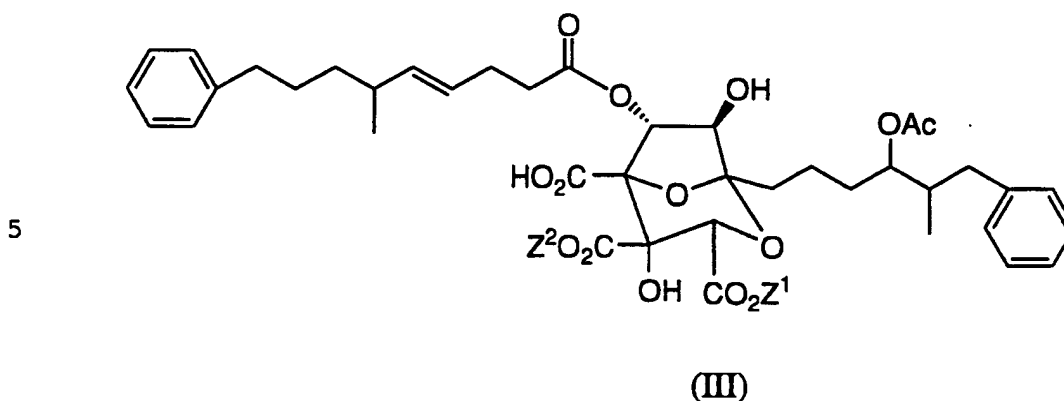


25 (III):

3. The compound of Claim 1 having structural formula

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- 33 -



10 selected from the group consisting of those wherein:

(a) Z1 is $-\text{CH}_2\text{CH}_3$ and Z2 is $-\text{CH}_2-\text{OC}-\overset{\text{O}}{\parallel}\text{C}(\text{CH}_3)_3$, and

15 (b) Z1 is $-\text{CH}_2\text{CH}_2\text{CH}_3$ and Z2 is $-\text{CH}_2-\text{OC}-\overset{\text{O}}{\parallel}\text{C}(\text{CH}_3)_3$.

4. A pharmaceutical composition comprising a nontoxic therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

20 5. A pharmaceutical composition comprising a nontoxic therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable nontoxic cationic polymer capable of binding bile acids in a non-reabsorbable form in the gastrointestinal tract and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition comprising a nontoxic therapeutically effective amount of a compound of Claim 1 in combination with a nontoxic therapeutically effective amount of a cholesterol lowering agent selected from the group consisting of:

- 30
- (a) HMG-CoA reductase inhibitor;
 - (b) HMG-CoA synthase inhibitor;
 - (c) squalene epoxidase inhibitor;
 - (d) probucol;
 - (e) niacin;

- 34 -

- (f) gemfibrozil; and
- (g) clofibrate.

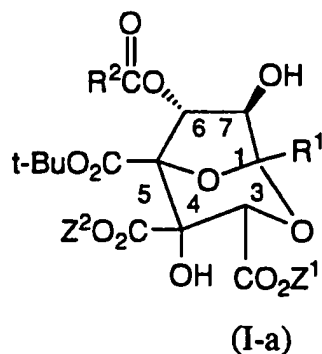
5 7. The composition of Claim 6 wherein the composition comprises a compound of Claim 1 and an HMG-CoA reductase inhibitor.

10 8. The composition of Claim 7 wherein the HMG-CoA reductase inhibitor is selected from lovastatin, simvastatin, pravastatin and fluvastatin.

15 9. A method of treating hypercholesterolemia comprising the administration to a subject in need of such treatment a nontoxic therapeutically effective amount of the compound of Claim 1.

20 10. A method of inhibiting squalene synthase comprising the administration to a subject in need of such treatment a nontoxic therapeutically effective amount of a compound of Claim 1.

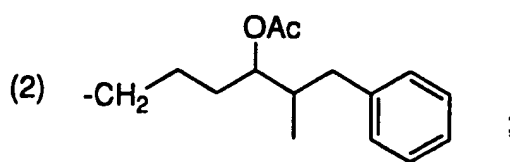
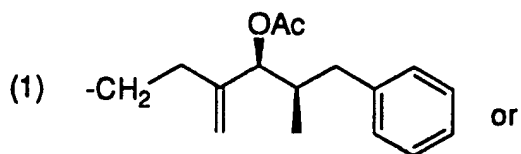
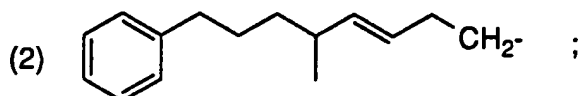
25 11. A process for making the compound of Claim 1 which comprises treating a compound of formula (I-a)



with trifluoroacetic acid,

wherein:

- 35 -

 R^1 is R^2 is

Z^1 is C_{1-3} alkyl or $-CH_2-CH=CH_2$;

Z^2 is (1) $-CHR^3-\overset{O}{\parallel}C-(O)_n-R^4$

wherein:

R^3 is $-H$ or C_{1-4} alkyl,

n is zero or 1, and

R^4 is

(a) C_{1-5} alkyl,

(b) phenyl, or

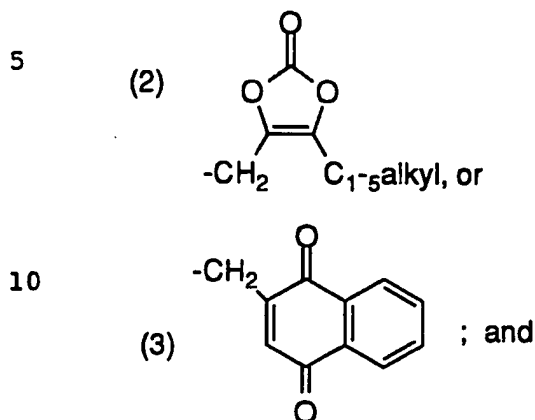
(c) phenyl substituted with X and Y, defined below,

or, when R^3 is C_{1-4} alkyl,

R^3 and R^4 are joined together to form a monocyclic or bicyclic ring system,

- 36 -

or, R^4 is joined together with the carbon to which R^3 is attached to form a monocyclic or bicyclic ring system, and R^3 represents the bond between R^4 and the carbon to which R^3 is attached,



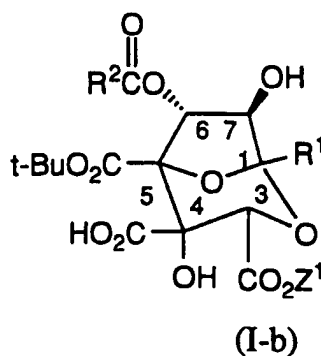
X and Y are each independently:

- 15 (1) hydrogen,
 (2) hydroxy,
 (3) halogen,
 (4) trifluoromethyl,
 (5) C₁₋₄alkyl,
 20 (6) C₁₋₄alkyl-O-,
 (7) C₁₋₄alkyl-C(O)-O-,
 (8) -CO₂C₁₋₄alkyl,
 (10) -CO₂H, or
 25 (11) nitro.

12. The process of Claim 11 wherein the compound of formula (I-a) is made by treating a compound of formula (I-b)

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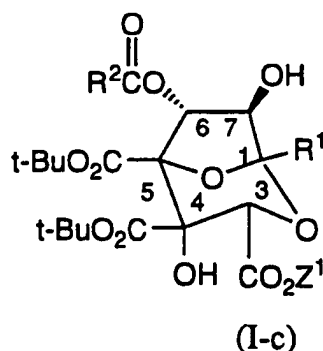
- 37 -



with:

- 10 (a) DBU and a compound of formula Z^2-X wherein X is -Br, -Cl or -I; or
 (b) N-methyl morpholine and isobutylchloroformate followed by treatment with an alcohol of formula Z^2-OH ; or
 (c) a coupling reagent and an alcohol of formula Z^2-OH ; or
 15 (d) Z^2O-N,N' -dialkyl-isourea.

13. The process of Claim 12 wherein the compound of formula (I-b) is made by treating a compound of formula (I-c)

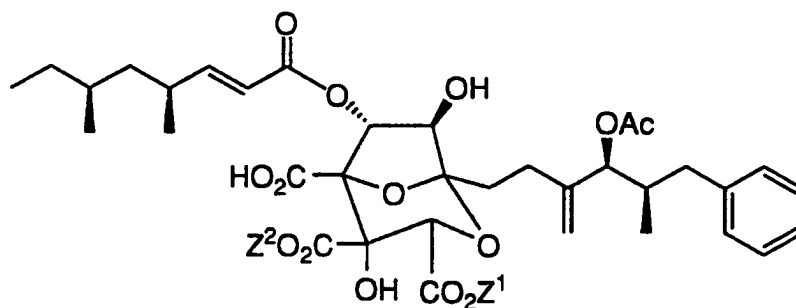


25 with a compound selected from the group consisting of thionyl chloride, tin(IV) chloride and hydrogen fluoride.

30 14. The process of Claim 1 for making a compound having structural formula (II):

- 38 -

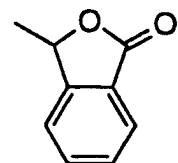
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(II)

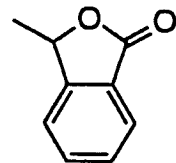
10 selected from the group consisting of those wherein:

- (a) Z^1 is CH_3 and Z^2 is $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- (b) Z^1 is $-\text{CH}_2\text{CH}_3$ and Z^2 is $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- 15 (c) Z^1 is $-\text{CH}_2\text{CH}_2\text{CH}_3$ and Z^2 is $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- (d) Z^1 is $-\text{CH}_2\text{-CH=CH}_2$ and Z^2 is $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- 20 (e) Z^1 is $-\text{CH}(\text{CH}_3)_2$ and Z^2 is $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- (f) Z^1 is $-\text{CH}_2\text{CH}_3$ and Z^2 is $-\text{CH}(\text{CH}_3)\text{OC}(=\text{O})\text{OCH}_2\text{CH}_3$;
- (g) Z^1 is $-\text{CH}_2\text{CH}_2\text{CH}_3$ and Z^2 is $-\text{CH}(\text{CH}_3)\text{OC}(=\text{O})\text{OCH}_2\text{CH}_3$;
- 25 (h) Z^1 is $-\text{CH}_2\text{CH}_3$ and Z^2 is $-\text{CH}(\text{CH}_3)\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- (i) Z^1 is $-\text{CH}_2\text{CH}_2\text{CH}_3$ and Z^2 is $-\text{CH}(\text{CH}_3)\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$;
- 30 (j) Z^1 is $-\text{CH}_2\text{CH}_2\text{CH}_3$ and Z^2 is



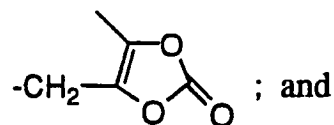
- 39 -

(k) Z¹ is -CH₂CH₂CH₃ and Z² is



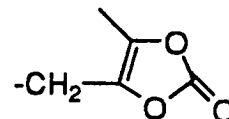
;

(1') Z¹ is -CH₂CH₂CH₃ and Z² is

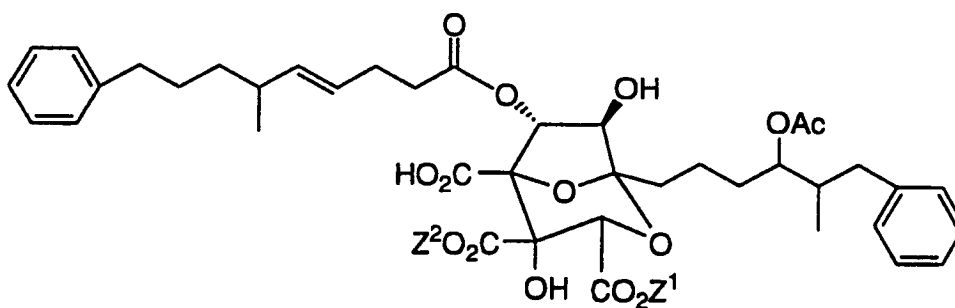


; and

(m) Z¹ is -CH₂CH₂CH₃ and Z² is



15. The process of Claim 11 for making a compound having structural formula (III):



(III)

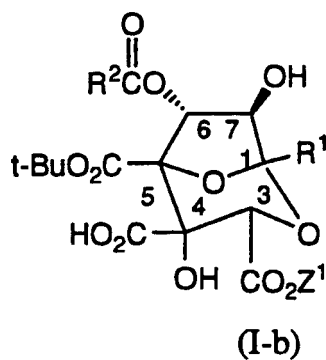
selected from the group consisting of those wherein:

(a) Z¹ is -CH₂CH₃ and Z² is -CH₂-OC(=O)-C(CH₃)₃; and

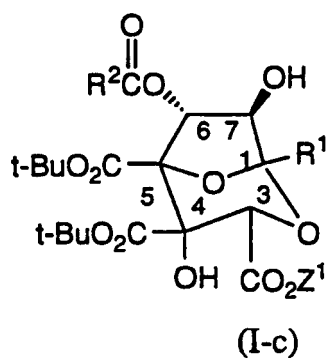
(b) Z¹ is -CH₂CH₂CH₃ and Z² is -CH₂-OC(=O)-C(CH₃)₃.

- 40 -

16. A process for making a compound of formula (I-b)



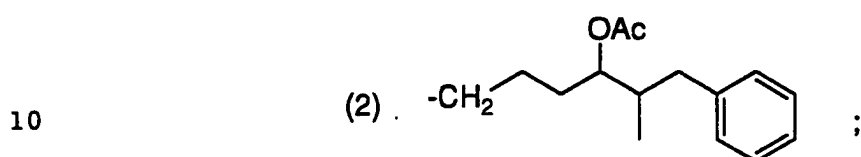
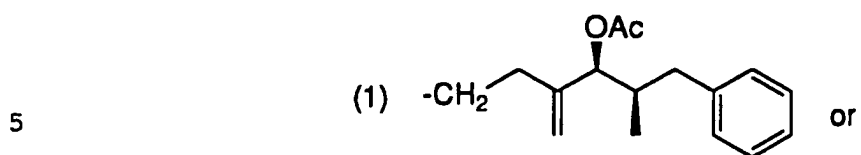
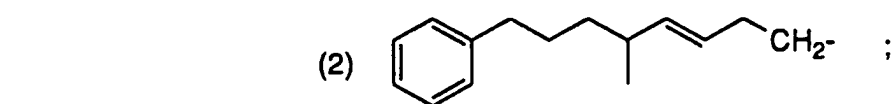
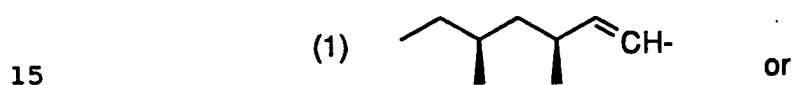
comprising treating a compound of formula (I-c)



with a compound selected from the group consisting of thionyl chloride, tin(IV) chloride and hydrogen fluoride,

- 41 -

wherein:

 R^1 is R^2 isand Z^1 is C_{1-3} alkyl or $-CH_2-CH=CH_2$.

25

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/10164

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/335; C07D 319/04

US CL :514/450,452; 549/363, 328,318,310,292,271,270,230,228

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/450,452; 549/363, 328,318,310,292,271,270,230,228

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 5,055,487 (Bartizal et al) 08 October 1991, see entire document.	1-10

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	* later documents published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search

10 FEBRUARY 1994

Date of mailing of the international search report

FEB 22 1994

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